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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/697,716	10/31/2003	H. William Bosch	029318-0977	8372

31049 7590 09/16/2008

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EXAMINER	
JEAN-LOUIS, SAMIRA JM	

ART UNIT	PAPER NUMBER
1617	

MAIL DATE	DELIVERY MODE
09/16/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/697,716	BOSCH ET AL.	
	Examiner	Art Unit	
	SAMIRA JEAN-LOUIS	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 May 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-41 and 43-108* is/are pending in the application.

4a) Of the above claim(s) *8,15,16,23-27 and 48-108* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,9-14,17-22 and 28-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *08/22/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

This Office Action is in response to the amendment submitted on 05/16/08. Claims 1-41 and 43-108 are currently pending in the application, with claim 42 having being cancelled and claims 8, 15-16, 23-27, and 48-108 having being withdrawn. Accordingly, claims 1-7, 9-14, 17-22, and 28-47 are being examined on the merits herein.

Receipt of the aforementioned amended claims, Information Disclosure Statement, and Affidavit is acknowledged and has been entered.

Applicants traversal of the provisional ODP rejection of claims 1, 4-7, 9-12, 14, 18-21, and 28-47 over claims 1-15, 17-20, and 22-41 of copending application 10/683154 is acknowledged, but since applicant did not put forth any arguments against this rejection, the ODP is maintained for reasons of record as stated in the previous office action and restated below for applicant's convenience.

Applicant's argument with respect to the term bioequivalency has been fully considered and is found persuasive. In view of applicant's amendment and applicant's Affidavit, such arguments are now moot. Consequently, the rejection of claim 43 under 35 U.S.C. § 112, second paragraph is thereby withdrawn.

Applicant's arguments against 102 (b) rejection and the fact that Krause does not explicitly teach the triamcinolone acetonide particles has been fully considered but is not found persuasive. First, Examiner would like to point out that the rejection was made under 35 U.S.C. 103 (a) and not found anticipatory. Second, Examiner would like to further point out that while Krause does not teach the size of the triamcinolone acetonide particles, Krause clearly teaches that the triamcinolone particles are encapsulated by polylactic acid (PLA) having the diameter below 1 μm. Because the triamcinolone particles are within the PLA capsule, the triamcinolone particles necessarily possess a diameter below 1 μm as well. Moreover, applicant's arguments that Examiner's statement on pg. 5-6 is a salient admission that the prior art's teaching reflects probabilities and possibilities are again non-persuasive. The claims were rendered obvious in view of the disclosure of Krause who clearly teaches that the triamcinolone particles are contained (i.e. encapsulated) by PLA so one of ordinary skill in the art would have found obvious that the particles encapsulated within the PLA are necessarily below 1 μm. Moreover, Krause was further used to demonstrate that loading of the particles not only signify that the particles were contained within the PLA capsule but that PLA was adsorbed unto the triamcinolone acetonide particles. Thus, in view of the teachings of Krause in view of Radhakrishnan and in further view of Unger, applicant's invention was indeed rendered obvious.

Applicant argues that Krause teaches the PLA particles as having a large surface area and thus one of ordinary skill would be left to interpret the possibilities of the

configuration of the composition and therefore would not consider the size of the particles as an inherent component of the triamcinolone particles. Such arguments are again not persuasive. Again, Examiner refers applicant to the fact that the claims were rejected under 103 (a) and not under 102. Radhakrishnan was provided to demonstrate that steroidal compositions can be combined with inflammatory agents and biorelevant media. Unger, on the other hand, was provided to demonstrate that particular anti-inflammatory drugs such as acetylsalicylate can be combined with triamcinolone and along with emulsifying agents. Thus, given that Krause teaches loaded PLA particles (i.e. contained within) of triamcinolone particles, one of ordinary skill would necessarily found obvious that the size of the encapsulated particles cannot be greater than the encapsulated shell. Thus, Krause in view of Radhakrishnan and in further view of Unger renders obvious applicant's invention.

Applicant's argument with respect to the rejection that is faulty due to the fact that the prior art reference does not teach a surface stabilizer adsorbed on the surface of triamcinolone particles has been considered but is not found persuasive. Examiner disagrees with such arguments as Examiner clearly stipulated on the record that the PLA was interpreted as a stabilizer. Given that applicant did not explicitly define that a stabilizer solely entails surfactants, Examiner construe that the PLA necessarily stabilize the triamcinolone particles as PLA affected the drug release and tissue distribution thereby stabilizing the drug in the human system. Thus, Krause in view of Radhakrishnan and in further view of Unger renders obvious applicant's invention.

For the foregoing reasons, the ODP rejection and the rejection of claims 1-7, 9-14, 17-22, and 28-47 under 103 (a) remains proper and is maintained. For applicant's convenience, the previous Office Action is restated below.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-5, 7 and 9-14 and 18-21 and 28-41, and 43-47 are rejected under 35 U.S.C. 103 (a) as being unpatentable over Krause et al. (Int. Journal of Pharmaceutics, 1985, Vol. 27, pg. 145-155, previously submitted) in view of Radhakrishnan (U.S. 5,049,389, previously submitted).

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Krause et al. teaches a composition of polylactic acid (PLA) (i.e. interpreted as a stabilizer given that applicant did not explicitly define a stabilizer as solely a surfactant) loaded with microcrystalline salts of triamcinolone acetonide (instant claims 1 -3; see abstract). It is also interpreted that loading of triamcinolone acetonide entails both encapsulation and adsorption of PLA unto triamcinolone acetonide given that fig. 2 denotes a transectional view of PLA nanoparticle with the triamcinolone crystals embedded in the center of the sphere and given that Krause suggests drug lying beneath the surface of the nanoparticles dissolve faster than drug crystals (i.e. crystalline form; instant claims 1 and 4) embedded in the center of the spheres (see pg. 145, microcrystalline form, abstract lines 8-10; see pg. 150, fig. 2 and pg. 152, lines 15-17). Krause et al. further teaches that the PLA nanoparticles have a mean diameter below 1 micron suggesting that the nanoparticle size of the triamcinolone acetonide necessarily are below 1 micron as well and this meets the limitation of claims 1 and 5 (see abstract). Krause et al. also teaches a drug content from 2.9% to 8.8% w/w (instant claim 10) and the inclusion of gelatin solution (i.e. additional stabilizer, instant claims 11-14) at 0.5% w/w and water as a suspension carrier (instant claim 9; see abstract and preparation of PLA nanoparticles-pg 147). Additionally, the composition of Krause et al. can include excipients (i.e. buffers; instant claim 9) and can be formulated for intravenous injection (i.e. liquid suspension; instant claim 7; instant claim 6 for

parenteral species; see abstract and pg. 147, drug release section, lines 3 and 11 and size distribution section, line 1). Krause et al. also teaches a suspension of various sized nanoparticles (i.e. triamcinolone of different sizes as well) in a solution (see size distribution, pg. 147 and table 1) that was injected into rats and subsequently dispersed to the liver and lung where high levels were still detected after 2 hours; this suggests that the ability of the nanoparticles to adhere to the surface of the liver and the lung is well enhanced (i.e. bioadhesive, instant claims 18-19; see pg. 153, table 2). Finally, Krause et al. discusses the fact that increasing PLA concentrations can result in an increase in viscosity (instant claim 44; see pg. 149, lines 16-17).

Krause et al. does not specifically teach a composition comprising triamcinolone acetonide in combination with other anti-inflammatory drugs or a composition that redisperses upon administration to a size less than 2000 nm. Moreover, Krause et al. does not specifically teach particles of triamcinolone acetonide with a particular percentage of Tmax, Cmax, AUC, viscosity or bioequivalency.

Radhakrishnan, however, teaches encapsulated steroidal compositions such as triamcinolone and its salts or esters in combination with non-steroidal drugs such as anti-inflammatory agents or antiviral drugs (i.e. acyclovir, non-elected species in claim 21, col. 20, line 43) or anti-hypertensive drugs (i.e. enalapril, verapamil, non elected species in claim 21, col. 20, lines 50-51; instant claims 20-21 col. 20, lines 14-15 and lines 31-32). Radhakrishnan further teaches the steroidal composition in deionized water (i.e. biorelevant media; instant claims 30-31; see col. 28, line 17). Radhakrishnan

also teaches encapsulated steroids of nanoparticle size where the mixture is filtered over a filter with pore size smaller than steroid crystals (i.e. non-encapsulated steroid crystals) usually of 0.1-1 micron filter. Subsequently, the filter is discarded leaving the micelle filtrate (i.e. encapsulated steroidal drug of 1 micron or less; see col. 14, lines 64-68).

Regarding the redispersibility of the triamcinolone particles, Krause et al. did teach that the particles do possess minute diameters. Consequently, it is well within the purview of one of ordinary skill in the art to conclude that given that that these drugs are small and are able to redistribute to the lung and liver as disclosed by Krause et al., it would have been obvious to one or ordinary skill in the art at the time of the invention that the triamcinolone particles would also redisperse at the same small size of less than 1 micron and this meets the limitation of claims 28-32.

Thus, to one of ordinary skill in the art at the time of the invention would have found it obvious to combine the anti-inflammatory agents of Radhakrishnan into the composition of Krause et al. since encapsulation of the drugs would lead to an improved delivery of the non-steroidal drug. Given that Krause et al. teaches a composition of polylactic acid (PLA) loaded with microcrystalline salts of triamcinolone acetonide, and Radhakrishnan et al. teaches that inflammatory drugs can be combined with encapsulated triamcinolone compositions for efficient drug target delivery, one of ordinary skill would have been motivated to combine an anti-inflammatory drug of

Radhakrishnan with the composition of Krause et al. with the expectation of providing a composition that is efficient in delivering drugs to targeted tissues.

Regarding the Tmax , Cmax, viscosity, bioequivalency and AUC of the triamcinolone particles as recited in claims 33-41 and 43-47, it is considered that one of ordinary skill in the art at the time of the invention was made would have found it obvious to conclude that the composition of Krause et al. combined with the anti-inflammatory agents of Radhakrishnan et al. would possess the same pharmacokinetic profiles as that disclosed by the applicant given that these characteristics are physical properties of the compound (i.e. nanoparticles of triamcinolone acetonide disclosed by Krause et al.) and such property is inseparable from the parent compound.

It is further noted that In re Best,195 USPQ 430, and In re Fitzgerald, 205 USPQ 594, discuss the support of rejections wherein the prior art discloses subject matter which there is reason to believe inherently includes functions that are newly cited or is identical to a product instantly claimed. In such a situation the burden is shifted to the applicants to "prove that subject matter shown to be in the prior art does not possess characteristic relied on" (205 USPQ 594, second column, first full paragraph).

Claims 6, 17, and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Krause et al. (Int. Journal of Pharmaceutics, 1985, Vol. 27, pg. 145-155, previously submitted) in view of Radhakrishnan (U.S. 5,049,389, previously submitted) as applied to claims 1-5, 7 and 9-14 and 18-21 and 28-41,

and 43-47 above and in further view Unger et al. (U.S. 5,542,935, previously submitted).

The Krause and Radhakrishnan references are as discussed above and incorporated by reference herein. However, Krause and Radhakrishnan do not address the aforementioned composition for topical administration. Similarly, Krause and Radhakrishnan did not specifically disclose specific anti-inflammatory agents such acetylsalicylate elected by applicant or the preferred stabilizers of applicant.

Unger et al., however, teaches encapsulation of therapeutic drugs (see abstract). Suitable therapeutic agents include steroidal drugs such as triamcinolone or triamcinolone acetonide in microspheres or liposomes (see col. 24, line 16 and col. 25, lines 9-11) and non-steroidal drugs such as aspirin and salicylates (i.e. acetylsalicylate, instant claim 22; see col. 25, lines 37-38). Unger et al. also teaches that if desired more than one therapeutic agent may be encapsulated for co-administration (see col. 23, lines 55-56 and col. 26, lines 34-37). Additionally, emulsifying agents and/or solubilizing agents may be used in conjunction with the liposome (i.e. capsule) including sodium lauryl sulfate (instant claim 17; see col. 23, lines 30-32 and line 40). Moreover, Unger et al. teaches that the encapsulated therapeutic drugs may be administered topically (instant claim 6; see col. 31, lines 15-17).

Thus, to one of ordinary skill in the art at the time of the invention would have found it obvious to utilize acetylsalicylate into the composition of Krause et al. and applied it topically given that Unger et al. teaches co-administration of salicylate with triamcinolone acetonide in encapsulated compositions. Likewise, it would have been obvious to utilize the emulsifying agent, sodium lauryl sulfate, since Unger et al. teaches its use in encapsulated compositions employing the steroid triamcinolone acetonide. Given that Krause et al. teaches a composition of polylactic acid (PLA) loaded with microcrystalline salts of triamcinolone acetonide, and Radhakrishnan et al. teaches that inflammatory drugs can be combined with encapsulated triamcinolone compositions for efficient drug target delivery, and Unger et al. teaches the use of the emulsifier, sodium lauryl sulfate and salicylate in conjunction with triamcinolone acetonide, one of ordinary skill would have been motivated to add the salicylate and emulsifier sodium lauryl sulfate of Unger et al. into the composition of Krause and Radhakrishnan with the expectation of providing a topical composition of Krause et al. that is stable and efficient in delivering drugs to targeted tissues.

Provisional Non-Statutory Double Patenting

Claims 1, 4-7, 9-12, 14, 18-21, and 28-47 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-15, 17-20, and 22-41 of copending Application No. 10683154 (hereinafter Liversidge US Patent Application No. '154). Although the conflicting claims are not identical, they are not patentably distinct from each other because both applications are

directed to a composition comprising effective nanoparticle size of a drug characterized by desirable pharmacokinetic profiles: effective particle size after redispersibility (see claims 28-32 of instant application vs. claims 22-26 of Liversidge '154), T_{max} (see claims 33-34 of instant application vs. claims 27-28 of Liversidge '154), C_{max} (see claims 35-36 of instant application vs. claims 29-30 of Liversidge '154), higher AUC rate (see claims 37-40 of instant application vs. claims 31-34 of Liversidge '154), bioequivalent (see claims 41-43 vs. claims 35-37 of Liversidge '154) as well as viscosity (see claims 44-47 of instant application vs. claims 38-41 of Liversidge '154), all of which are due to the size of the drug.

More specifically, claims 1, 4-7, 9-12, 14, 18-21, and 28-47 of the instant application are directed to a composition comprising: sterol (triamcinolone acetonide being the elected species) with particle size less than 2000nm and a surface stabilizer.

Claims 1-15, 17-20, and 22-41 of the conflicting Liversidge '154 application are directed to a composition comprising an anti-fungal drug with particle size less than 2000nm and a surface stabilizer (other than non-ionic).

As a result, although claims 1, 4-7, 9-12, 14, 18-21, and 28-47 of the instant application are not identical to claims 1-15, 17-20, and 22-41 of the conflicting Liversidge '154 application, the aforementioned claims are not patentably distinct from each other because said claims comprise nanoparticle drugs of a size less than 2000nm characterized by increased bioavailability and redispersibility, which results in better efficacy of both drugs. Thus, one of ordinary skill would have the motivation to use "any" nanoparticulate of a drug with a stabilizer and would have a reasonable

expectation that such a substitution would yield predictable results, including an enhanced pharmacokinetic profile. Thus, the aforementioned claims of the instant application are substantially overlapping in scope as discussed hereinabove and are prima facie obvious over the cited claims of corresponding application No. 10, 683, 154.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samira Jean-Louis whose telephone number is 571-270-3503. The examiner can normally be reached on 7:30-6 PM EST M-Th.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/S. J. L. /

Examiner, Art Unit 1617

09/05/2008

/SREENI PADMANABHAN/

Supervisory Patent Examiner, Art Unit 1617